REMARKS

Claims 1-17 and 19-40 are pending. Claims 1, 35, 36, and 38 are amended herein to clarify the claimed subject matter. Claims 19 and 24-33 are withdrawn from consideration and are canceled herein without prejudice. Claims 3, 17, 21, 34, 37, 39, and 40 are canceled herein without prejudice. Accordingly, instant claims 1, 2, 4-16, 20, 22-23, 35-36, and 38 are presently under consideration.

Support for the amendments to claims is found throughout the specification and in the original claims. More particularly, support for amendment to claim 1 is found, for example, in original claims 1 and 3 and in paragraphs [0017]-[0018], [0023]-[0025], [0038], [0043], [0052]-[0056], [0068], and [0070] and Figure 1 of United States Application Publication No. 2006-0130852, which corresponds to the instant application. For the sake of clarity, all support identified hereinafter refers to paragraph numbers in the above-indicated published application. Support for amendment to claim 35, 36, and 38 is found, for example, in original claim 1. No issue of new matter is introduced via these amendments.

Claim Objections

Claims 24 and 34 are objected for the presence of informalities (claim 24) or for depending from a withdrawn claim (claim 34). Claims 24 and 34 are canceled herein, thereby obviating any rejection of these claims.

Rejections under 35 U.S.C. § 112

Claims 1-16, 20-23, and 34-40 are rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was allegedly not enabled by the specification. Claims 3, 21, 34, 37, 39, and 40 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1-16, 20-23, and 34-40 is traversed.

The Office Action acknowledges that the specification is enabling for the claimed method using cells isolated from bone marrow aspirate, but allegedly fails to provide sufficient enablement for the claimed method using a composition of mesenchymal stem

cells. Claim 1 is amended to be directed to a method of treating a soft skeletal tissue injury in a patient the method comprising: culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury.

Contrary to the assertions of the Office Action, the specification does present sufficient guidance on which basis an ordinarily skilled practitioner would be able to obtain mesenchymal stem cells (MSCs) from bone marrow aspirate. See, for example, paragraphs [0054]-[0056]. Moreover, such a practitioner would be familiar with techniques for isolation of MSCs in light of reference to the Rickard et al. (1996) reference in paragraph [0054] and general knowledge in the field. Applicant, therefore, asserts that an ordinarily skilled artisan would be able to isolate MSCs from bone marrow aspirate as taught in the instant specification and such an endeavor would not require undue experimentation.

Moreover, responsive to the assertions of the Office Action that the presence of MSCs, even after expansion, has yet to be confirmed, Applicant asserts that the specification explicitly demonstrates that MSCs are present after semi-purification from bone marrow by Ficoll centrifugation. See, for example, Figure 1 and paragraph [0043]. The Examiner is also respectfully directed paragraphs [0060]-[0062] and [0070]. Furthermore, the specification also describes clinical evidence of soft tissue repair following MSC implantation. See, for example, paragraph [0071].

In light of the above, Applicant asserts that the instant claims are enabled by the specification. That being the case, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-16, 20-23, and 34-40 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement.

Claim 17 is rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was allegedly not enabled by the specification. Claim 17 is canceled

herein, thereby obviating any rejection of this claim. In view of the clarifying amendments to the claims, therefore, the rejection of claim 17 is traversed.

Claims 1-17, 20-23, and 34-40 are rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Claims 3, 17, 21, 34, 37, 39, and 40 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection, as it applied to claims 1-17, 20-23, and 34-40 is traversed.

Claim 1 is amended to be directed to a method of treating a soft skeletal tissue injury in a patient the method comprising: culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury. In light of the above, the claims are amended to reflect that the claimed method calls for, *inter alia*, "culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition ...". Accordingly, the method calls for administering the composition to the site of soft skeletal tissue injury of the patient.

Contrary to the assertions of the Office Action, the specification presents ample description of what is meant by "bone marrow supernatant". In short, "bone marrow supernatant" is the fluid phase collected after centrifugation of the aspirated bone marrow. Support for the term "bone marrow supernatant" is found throughout the specification. See, for example, paragraph [0025]. A description of how to obtain bone marrow supernatant is found, for example, at paragraph [0077], wherein bone marrow supernatant is generated by spinning down bone marrow aspirate and collecting the supernatant, which is thereafter frozen. Paragraph [0090] details resuspending MSCs in previously thawed platelet-rich plasma (PRP) or marrow supernatant. Applicant asserts,

therefore, that the guidance presented in the specification, in combination with basic knowledge in the field, describes the term "bone marrow supernatant" in sufficient detail to evidence that the inventors were in possession of the claimed invention at the time of filing.

The comments of the Office Action pertaining to characterization of cell populations comprising MSCs are duly noted. Responsive thereto, Applicant asserts that MSCs are defined in the specification by the following properties: 1) morphological characteristics, see, for example, Figure 1 and paragraph [0060] and paragraph [0122], wherein MSCs are shown and described as "round shiny objects adhered to the flask"; 2) behavioral characteristics, see, for example, paragraph [0122], wherein the ability to adhere is identified as a distinguishing feature of stem cells; 3) multipotency, see, for example, paragraph [0018], wherein the ability of MSCs to differentiate into several different cell types is described as a distinctive feature of MSCs; and 4) the presence of certain cell surface markers in some species, see, for example, paragraph [0018]. In light of the above, Applicant asserts that the characteristics of MSCs are described in sufficient detail in the specification to be identified and quantified.

It is, therefore, evident that the inventors were in possession of the invention as instantly claimed at the time of filing of the present application. That being the case, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-17, 20-23, and 34-40 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

Claims 1-17, 20-23, and 34-40 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Claims 3, 17, 21, 34, 37, 39, and 40 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims, the rejection, as it applied to claims 1-17, 20-23, and 34-40 is traversed.

Rejections under 35 USC § 102

Claims 1-9, 12-14, 16, and 22 are rejected under § 102(b) as allegedly anticipated by Herthel (2001, Proc Am Assoc Equine Practnrs 47:319-321). Claim 3 is canceled herein, thereby obviating any rejection of this claim. In view of the clarifying

amendments to the claims and Applicant's arguments presented herein, this rejection is respectfully traversed.

Instant claim 1 is directed to a method of treating a soft skeletal tissue injury in a patient the method comprising, *inter alia*, culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury.

In contrast, Herthel fails to teach or suggest culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant to a site of soft skeletal tissue injury to promote regeneration of soft skeletal tissue at the site. Herthel, therefore, fails to teach two recited elements of the claims and thus fails to anticipate the instantly claimed invention.

In view of the clarifying amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-9, 12-14, 16, and 22 under 35 U.S.C. §102 and withdraw the rejection.

Claims 1-6, 12-14, 22, and 34-36 are rejected under § 102(b) as allegedly anticipated by Awad (1999, Tissue Engineering 5:267-277). Claims 3 and 34 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, this rejection is respectfully traversed.

As detailed herein above, instant claim 1 is directed to a method of treating a soft skeletal tissue injury in a patient the method comprising, *inter alia*, culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant,

or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury.

Awad, on the other hand, fails to teach or suggest a method of treating a soft skeletal tissue injury in a patient comprising culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. Contrary to the assertions of the Office Action and as detailed herein above, the specification does define what is meant by "bone marrow supernatant". See, for example, paragraphs [0025], [0077], [0090] of the specification and arguments presented herein above, which are incorporated herein in their entireties. In light of the above, an ordinarily skilled practitioner would not view "a gel collagen solution" of Awad as equivalent to "a bone marrow supernatant" as taught in the instant specification. As a consequence of this distinction, Awad fails to teach a recited element of the claims and thus fails to anticipate the instantly claimed invention.

In view of the clarifying amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-6, 12-14, 22, and 34-36 under 35 U.S.C. §102 and withdraw the rejection.

Claims 1-6, 12-15, 21, 23, 34-36, 39, and 40 are rejected under § 102(b) as allegedly anticipated by United States Patent Number (USPN) 5,811,094. Claims 3, 21, 34, 39, and 40 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, this rejection is respectfully traversed.

As detailed herein above, instant claim 1 is directed to a method of treating a soft skeletal tissue injury in a patient the method comprising, *inter alia*, culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid

suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury.

USPN 5,811,094 fails to teach or suggest a method of treating a soft skeletal tissue injury in a patient comprising culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. In that the specification does define what is meant by "bone marrow supernatant", an ordinarily skilled practitioner would not view "a collagen solution" of USPN 5,811,094 as equivalent to "a bone marrow supernatant" as taught in the instant specification. See above for additional arguments, which are incorporated herein in their entireties. In light of this significant distinction, USPN 5,811,094 fails to teach a recited element of the claims and thus fails to anticipate the instantly claimed invention.

In view of the clarifying amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-6, 12-15, 21, 23, 34-36, 39, and 40 under 35 U.S.C. §102 and withdraw the rejection.

Claims 1-7, 12-14, 16, 21-23, 34-36, 39, and 40 are rejected under § 102(e) as allegedly anticipated by USPN 6,835,377. Claims 3, 21, 34, 39, and 40 are canceled herein, thereby obviating any rejection of these claims. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, this rejection is respectfully traversed.

As stated above, instant claim 1 is directed to a method of treating a soft skeletal tissue injury in a patient the method comprising, *inter alia*, culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant, wherein said administering promotes regeneration of the soft skeletal tissue at the site of soft skeletal tissue injury.

USPN 6,835,377 fails to teach or suggest a method of treating a soft skeletal tissue injury in a patient comprising culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. As detailed herein above, the specification defines what is meant by "bone marrow supernatant". Given the teachings of the instant specification and common knowledge, an ordinarily skilled practitioner would not view "a collagen solution" of USPN 6,835,377 as synonymous with "a bone marrow supernatant" as taught in the instant specification. See above for additional arguments, which are incorporated herein in their entireties. That being the case, USPN 6,835,377 fails to teach a recited element of the claims and thus fails to anticipate the instantly claimed invention.

In view of the clarifying amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-7, 12-14, 16, 21-23, 34-36, 39, and 40 under 35 U.S.C. §102 and withdraw the rejection.

Rejections under 35 USC § 103

Claims 34, 37, and 38 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over USPN 5,811,094 in view of Herthel (*supra*). Claims 34 and 37 are canceled herein, thereby obviating any rejection of these claims. In view of Applicant's arguments presented herein, the rejection, as it applied to claims 34, 37, and 38, is respectfully traversed.

As detailed herein above, the combined teachings of USPN 5,811,094 and Herthel fail to teach or suggest a method of treating a soft skeletal tissue injury in a patient comprising culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells in a liquid suspension of bone marrow supernatant, or enriched for mesenchymal stem cells and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. In light of the above, it is apparent that USPN 5,811,094 and Herthel fail to teach or suggest a recited element of

the instant claims. Arguments presented herein above with regard to the deficiencies of these references are also incorporated herein in their entireties.

Moreover, neither reference when considered alone or in combination demonstrates any appreciation of the advantages conferred by resuspending a composition enriched for MSCs or MSCs and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. Such advantages are described, for example, in paragraph [0025] of the instant specification, wherein media suitable for use in liquid suspensions are described as containing appropriate biological signals to encourage the differentiation of the mesenchymal stem cells into cell types that are useful to the regeneration of soft skeletal tissue injuries (e.g., tenocytes in the case of regeneration of tendons), but more importantly, to discourage the differentiation of the cells into cell types that are not useful (e.g., bone tissue) and thereby lead to deleterious mineralization as demonstrated using the Herthel method. See paragraphs [0003] and Example 4 (paragraphs [0181]-[0184] in particular) of the instant specification for additional details pertaining to the defects of the Herthel method. That being the case, USPN 5,811,094 when considered alone or in combination with Herthel fails to render obvious the present claims.

In view of the above, Applicant deferentially requests that the rejection of claims 34, 37, and 38 under 35 U.S.C. § 103(a) as allegedly unpatentable over USPN 5,811,094 in view of Herthel be reconsidered and withdrawn.

Claims 34, 37, and 38 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over USPN 6,835,377 in view of Herthel (*supra*). Claims 34 and 37 are canceled herein, thereby obviating any rejection of these claims. In view of Applicant's arguments presented herein, the rejection, as it applied to claims 34, 37, and 38, is respectfully traversed.

As asserted above, the combined teachings of USPN 6,835,377 and Herthel fail to teach or suggest a method of treating a soft skeletal tissue injury in a patient comprising culturing bone marrow cells in vitro to generate a composition enriched for mesenchymal stem cells and administering to a site of soft skeletal tissue injury of the patient the composition enriched for mesenchymal stem cells <u>in a liquid suspension of bone marrow supernatant</u>, or enriched for mesenchymal stem cells and tenocytes derived therefrom <u>in a</u>

liquid suspension of bone marrow supernatant. In light of the above, it is apparent that the combined teachings of USPN 6,835,377 and Herthel fail to teach or suggest a recited element of the instant claims. Arguments presented herein above with regard to the deficiencies of these references are also incorporated herein in their entireties.

Moreover, neither reference when considered alone or in combination demonstrates any appreciation of the advantages conferred by resuspending a composition enriched for MSCs or MSCs and tenocytes derived therefrom in a liquid suspension of bone marrow supernatant. As mentioned above, such advantages are described, for example, in paragraph [0025] of the instant specification, wherein media suitable for use in liquid suspensions are described as containing appropriate biological signals to encourage the differentiation of the mesenchymal stem cells into cell types that are useful to the regeneration of soft skeletal tissue injuries (e.g., tenocytes in the case of regeneration of tendons), but more importantly, to discourage the differentiation of the cells into cell types that are not useful (e.g., bone tissue) and lead to detrimental mineralization as demonstrated using the Herthel method. Paragraphs [0003] and Example 4 (paragraphs [0181]-[0184] in particular) of the instant specification present additional information pertaining to the defects of the Herthel method. That being the case, USPN 6,835,377 when considered alone or in combination with Herthel fails to render obvious the present claims.

In view of the above, Applicant deferentially requests that the rejection of claims 34, 37, and 38 under 35 U.S.C. § 103(a) as allegedly unpatentable over USPN 6,835,377 in view of Herthel be reconsidered and withdrawn.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form

of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Enclosure: Petition for a Three Month Extension of Time